Supplemental Material

Methods

Echocardiographic Analysis

At least 3 consecutive beats were recorded for each view, and images were stored for offline analysis (Image Arena 4.6; TomTec, Unterschleissheim, Germany). Analysis of the echocardiographic images were performed by 3 experienced operators blinded to the final diagnosis and to the 99mTc-PYP and clinical data, with review by an expert echo reader. Left ventricular (LV) chamber morphology was assessed by following the most recent American Society of Echocardiography/European Association of Cardiovascular Imaging Guidelines (ASE/EACVI), as were measurements of LV and LA volumes. LV mass and LV mass index were calculated using Devereux's formula (2), relative wall thickness (RWT) was calculated as: 2 × posterior wall thickness in diastole/LVEDD (2 × PWTd/LVEDD), eccentricity index as IVSd/PWTd, myocardial volume as LV mass/1.05, and MCF as stroke volume/myocardial volume. LVEF was calculated with the biplane Simpson's method from volumes acquired in both the 4- and 2-chamber views. Diastolic parameters were measured as per the most recent ASE/EACVI guidelines. The tricuspid annular planar systolic excursion (TAPSE) was assessed with M-mode in the 4-chamber view. RV systolic excursion velocity (s') was also measured using tissue Doppler imaging of lateral tricuspid annulus.

Mayo TCAS score

Age (60-69, 70-79, ≥ 80: +2, +3, +4 points respectively), male sex (+2), relative WT > 0.57 (+2), posterior WT ≥ 12 mm (+1), EF < 60% (+1), and hypertension diagnosis (-1).

Regression Model

Least absolute shrinkage and selection operator (LASSO) regression is a type of linear regression that uses shrinkage. Shrinkage is where data values are shrunk towards a central point, like the mean. The lasso procedure encourages simple, sparse models (i.e. models with fewer parameters). This particular type of regression is well-suited for models showing high levels of multicollinearity or when you want to automate certain parts of model selection, like variable selection/parameter elimination. This penalizes the model to reduce overfitting and has the added benefit of deleting “unimportant” predictors. The penalty parameter for LASSO was chosen using cross-validation (10-fold) across different penalties to see which one produces the best model deviance.

We started with 36 echo parameters (table) and age. We excluded 5 for having > 25 (approximately 15% of the data) missing observations. We set a cutoff for Pearson’s correlation at 0.85. For crossing this threshold, 9 variables were removed. Bag imputation was on the remaining variables to fill in the few missing observations present. This leaves us with 23 predictors, which is too many to fit a standard logistic regression model with given the number of events/non-events that we have in our response. Therefore, LASSO logistic regression was used. This will penalize our model somewhat (to reduce overfitting) and has the benefit of deleting “unimportant” predictors. The penalty parameter for LASSO can be chosen a number of ways, but the simplest is to use cross-validation (10-fold) across different penalties to see which one produces the best model deviance. This is, however, a very unstable process as it depends on where the folds are cut, so we did this 1000 times and picked the mean

penalty. Across the 1000 models generated, they were all fairly similar. Most variables were consistently eliminated and the ones that weren't tended to bubble around the same regression coefficient values.

Results

Logistic Regression

The final logistic regression model (PYP positive/negative= 0.17 posterior wall diameter + 0.03 Age + 0.17 midline basal LS).

Tables

Supplementary Table S1: Strain by view.

Midwall 4c LS (%)	-12.0 ± 4.2	-8.8 ± 3.0	<0.001
Midwall 2c LS *	-11.8 ± 4.6	-8.8 ± 3.4	<0.001
Midwall 3c LS *	-11.4 ± 4.2	-8.7 ± 3.0	<0.001

endo, endocardial; LS, longitudinal strain; RELAS, relative apical sparing ratio; SAB, septal apical to base longitudinal strain ratio; 2c, 2 chamber view; 3c, 3 chamber view; 4c, 4 chamber view.

Data is displayed as mean ± standard deviation for normal distributed data, median [interquartile range] for non-parametric data.

* parameter not measured in entire cohort as detailed in text

Net Reclassification Index Tables

Supplementary Table S2 A & B: Reclassification of Study Participants into Groups With and Without ATTR Cardiac Amyloidosis by using a TCAS cut-off of 6 compared to a inferolateral wall thickness of 14 mm.

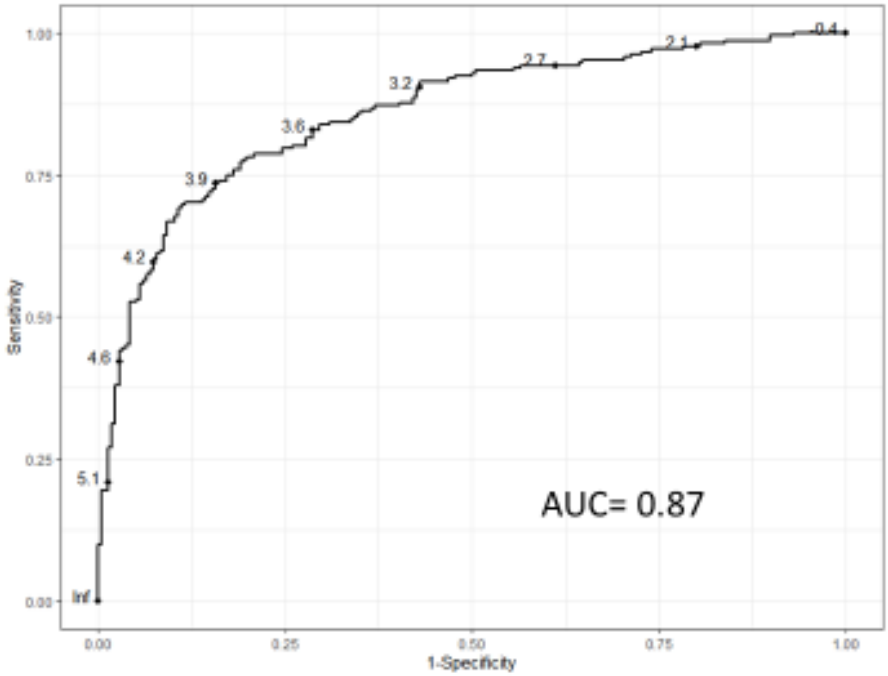
Non-ATTR	TCAS < 6	TCAS > 6
PWD<14 mm	104	66
PWD>14 mm	31	71

ATTR	TCAS < 6	TCAS > 6
PWD<14 mm	18	41
PWD>14 mm	3	256

NRI [95% CI]: -0.009 [-0.089 - 0.070]; p-value: 0.82

Figures

Supplementary Figure S1: Prediction of ATTR-CM from LASSO binary logistic regression model.


Sensitivity
1-Specificity
0.00
0.25
0.50
0.75
1.00
Inf
5.1
4.6
4.2
3.9
3.6
3.2
2.7
2.1
0.4
AUC= 0.87